Metal-Free Photoinduced C(sp^3)–H Borylation of Alkanes

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Summary Paragraph

Boronic acids and their derivatives are some of the most useful reagents in the chemical sciences,[1] with applications spanning pharmaceuticals, agrochemicals, and functional materials. Catalytic C–H borylation is a powerful method for introducing these and other boron groups into organic molecules.[1-3] These reactions have traditionally relied on precious metal catalysts for C–H bond cleavage and, as a result, display high selectivity for borylation of aromatic C(sp^2)–H bonds over aliphatic C(sp^3)–H bonds.[4] Here, we report a mechanistically distinct, metal-free, borylation using hydrogen atom transfer (HAT) catalysis,[5] where homolytic cleavage of C(sp^3)–H bonds produces alkyl radicals that are borylated by direct reaction with a diboron reagent. The reaction proceeds by violet-light photoinduced electron transfer between an *N*-alkoxyphthalimide-based oxidant and a chloride HAT catalyst. Unusually, stronger methyl C–H bonds are borylated preferentially over weaker secondary, tertiary and even benzylic C–H bonds.

Main Text

The importance of organoboron compounds has triggered intensive research into new methods to introduce boron into organic molecules, the most direct of which is C–H borylation (Fig. 1a).[2,3] This approach benefits from introducing a synthetically valuable boron moiety into inherently unreactive feedstock chemicals by substitution of ubiquitous C–H bonds. Whilst C(sp^2)–H borylation of aromatic compounds is well established (e.g., using iridium catalysts),[6,7] C(sp^3)–H borylation of alkanes is less developed.[4] The majority of reported C(sp^3)–H borylations employ activated substrates[8-13] or those possessing heteroatom directing groups,[14-18] whereas borylations of non-activated C(sp^3)–H bonds require the use of precious-metal catalysts and harsh reaction conditions.[19-23] Furthermore, the higher reactivity of aromatic C–H bonds

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prohibits selective borylation of non-activated C(sp^3)–H bonds in the presence of sterically accessible C(sp^2)–H bonds.[23]

We envisioned an alternative C(sp^3)–H borylation using a hydrogen atom transfer (HAT) strategy.[5] Here, the C–H bond is cleaved by intermolecular reaction with a heteroatom-centred radical (X$^\bullet$), rather than a metal catalyst, and subsequent homolytic substitution of a diboron reagent by the resulting alkyl radical intermediate forms the C–B bond (Fig. 1b). An important feature of this proposed mechanism is that regioselectivity should be determined by the bond dissociation energy (BDE) of the C–H bond, thus high selectivity for borylation of alkyl groups [BDE = 98 kcal mol^{-1} for cyclohexyl–H][24] over aromatic rings [BDE = 113 kcal mol^{-1} for phenyl–H][25] will occur.

Herein, we report a photoinduced borylation of non-activated C(sp^3)–H bonds using chloride as a HAT catalyst. The use of a radical-mediated strategy allows a wide range of functionalised alkanes to be borylated under exceptionally mild conditions (ambient temperature, violet-light irradiation) and circumvents the high C(sp^2)–H selectivity inherent in transition metal-catalysed borylations. Furthermore, direct photoexcitation of an *N*-alkoxyphthalimide oxidant allows these reactions to occur in the absence of a metal catalyst,[26] therefore providing the first examples of room temperature and metal-free C(sp^3)–H bond borylations.

Our initial design plan for C–H borylation was inspired by our decarboxylative borylation of *N*-hydroxyphthalimide esters **1** with bis(catecholato)diboron [**2**, $B_2(cat)_2$] (Fig. 1c).[27] During that process, photoinduced electron transfer (PET) under blue-light irradiation provided phthalimide radical anion intermediates **3**. In the case of aliphatic esters (R^1 = alkyl), decarboxylative fragmentation furnished phthalimide anion **4** and an alkyl radical **5**, which was borylated by reaction with $B_2(cat)_2$ to form boronic ester **6**. We reasoned that if *N*-alkoxyphthalimides **7** were used in place of esters **1**, fragmentation of the radical anion intermediate **8** by N–O bond cleavage would produce a highly reactive oxygen-centred radical

(**9**) that is capable of cleaving strong C(sp^3)–H bonds via HAT.[28-30] Intermolecular HAT between **9** and an alkane **10** (R^2 = alkyl) would generate alcohol **11** and alkyl radical **12**, which would be rapidly borylated by reaction with $B_2(cat)_2$ to give C–H borylation product **13**.[31]

We postulated that the nature of the oxygen-centred radical **9** would be crucial for successfully implementing our reaction design. For productive C–H borylation, **9** must (i) be stable to β-fragmentation to alkyl radicals; (ii) be electrophilic, therefore favouring reaction with hydridic aliphatic hydrogen atoms over direct reaction at the electrophilic boron atoms of **2**; and (iii) form strong O–H bonds (BDE >100 kcal mol^{-1}) upon HAT, thus allowing borylation of strong C(sp^3)–H bonds. Considering these requirements, we selected *N*-(2,2,2-trifluoroethoxy)phthalimide (**14**) (Fig. 1d) as this would provide the electrophilic 2,2,2-trifluoroethoxy radical, which has previously been reported to cleave strong C(sp^3)–H bonds.[32]

Our initial investigations focused on the borylation of norbornane (**15**), which was irradiated in the presence of $B_2(cat)_2$ and alkoxyphthalimide **14** in acetonitrile (Fig. 1d), but unfortunately no C–H borylation product was observed (Fig. 1d, entry 1). Based on a recent report by Zuo and co-workers on alkoxy radical-mediated C(sp^3)–H functionalisation using cerium catalysis,[32] we investigated the effect of cerium salts on the borylation reaction (Table S1).[33] Pleasingly, in the presence of cerium(IV) chloride tetraethylammonium chloride complex [$CeCl_6(NEt_4)_2$], irradiation with violet-light gave boronic ester **17** in 36% yield (Fig. 1d, entry 2). Surprisingly, a control experiment with just tetraethylammonium chloride (NEt_4Cl) as catalyst resulted in the formation of **17** in a similar yield, suggesting that chloride is catalysing the reaction (Fig. 1d, entry 3). Further improvements were made through analysis of a range of other chloride sources (Table S2), with 20 mol% *B*-chlorocatecholborane [ClB(cat)] proving optimal, enabling formation of **17** in 61% yield (Fig. 1d, entry 4). Due to the instability of the initially formed catechol boronic ester **16** to hydrolysis, in situ transesterification to the stable pinacol boronic ester **17** was performed prior to isolation in all cases.

With these metal-free C(sp^3)–H borylation conditions, we proceeded to explore the scope of the reaction (Fig. 2). Unfunctionalised cyclic alkanes, which are commonly employed as solvents in metal catalysed C–H borylations due to their low reactivity,[23] were successfully borylated to provide alkylboronic esters **17**–**22**. In addition, borylation of cycloalkanes functionalised with halides or nitrile groups was also possible (**23**–**25**). High regio- and diastereoselectivities were obtained in the reactions of norbornane (**17**), *trans*-decalin (**23**), and *exo*-2-chloronorbornane (**24**), with no borylation of tertiary C–H bonds observed. Cyclopentane carbonitrile (**26**) reacted selectively at the methylene distal to the electron-withdrawing nitrile group.

We next investigated the effectiveness of our protocol for the borylation of acyclic alkanes. While a variety of unfunctionalised substrates were successfully borylated (**26**-**31**), we were surprised to observe selective borylation of methyl groups over methylene groups. This selectivity is the opposite to that expected in homolytic cleavage of C–H bonds via HAT, where selectivity is typically determined by the strength of the C–H bond, thus favouring reaction at methylene (BDE ~99 kcal mol^{-1}) over methyl groups (BDE ~101 kcal mol^{-1}).[25] Pentane was borylated with a methyl/methylene selectivity of approximately 1:1 (**26**), whereas for substrates containing sterically hindered methylene groups, complete methyl selectivity was observed (**28**-**31**). Interestingly, 2,2,4,4-tetramethylpentane (**31**) was borylated efficiently, which represents the first example of a borylation of a *tert*-butyl group in the absence of directing groups.[11,22,26] Selective reaction at sterically hindered methyl groups was also observed for various functionalised acyclic alkanes, including those containing halides (**32**-**36**), protected amines (**37**-**38**), and nitriles (**39**). The regioselectivity appeared to be sensitive to electronic effects, with no borylation observed at sterically unhindered methylene groups proximal to electron-withdrawing groups (**33**, **36**-**39**). For substrates possessing even weaker methine C–H bonds, no tertiary boronic ester products where observed in any cases.

We also tested substrates possessing both C(sp^3)–H bonds and sterically unhindered aromatic C(sp^2)–H bonds, which give high selectively for aromatic C–H borylation with iridium catalysis.[23] Isopropylbenzene

(**40**) was borylated with complete selectivity for the methyl groups over both the aromatic and the much weaker benzylic C–H bonds. Similar selectivity was observed for several other isopropylbenzene derivatives (**41**-**42**); notably 4-isopropyltoluene (**41**), which possesses an unhindered benzylic methyl group.[8] The reaction was extended to sterically hindered methyl groups of *tert*-butylbenzenes (**43**-**44**), which are unreactive under metal-catalysed conditions. Borylation of C(sp^3)–H bonds distal to aromatic rings was also possible, including neopentyl (**45**) and cyclohexyl benzene (**46**), and various heteroaromatic carboxylate esters (**47**-**48**). In addition, terminal alkenes were tolerated, with 4,4-dimethyl-1-pentene reacting at the *tert*-butyl group to provide boronic ester **49**. More complex substrates were also successfully borylated, including ibuprofen methyl ester (**50**), a galactose derivative (**51**), and phthalimide-protected derivatives of the amino acids leucine (**52**) and *tert*-leucine (**53**). Although reactions were routinely run using 10 equivalents of alkane, the excess alkane could be recovered in >80% yield, and in several cases we showed that 5 or 3 equivalents could also be employed without a substantial reduction in yield (**17**, **29**, **30**, **32**, **36** and **53**). Alternatively, improved yields could be obtained with 20 equivalents of alkane (**17**). Usually, C(sp^3)–H borylations require substrates be used in excess, and it was only very recently that Hartwig was able to overcome this limitation by using a modified iridium/phenanthroline ligand system.[23] This is especially valuable for complex substrates. Therefore, we tested our methodology using the alkane as the limiting reagent and found that, under slightly modified conditions, the complex amino acid-derived product **53** could be isolated in comparable yield with 85% recovery of unreacted alkane (for further alkane stoichiometry studies, see Supplementary Information, Section 2.7).

Organosilanes are an important compound class that are used extensively in organic synthesis and materials science. Suginome and co-workers demonstrated that iridium-catalysed C(sp^3)–H borylation of methyl silanes provides a convenient and direct method to access synthetically useful (borylmethyl)silanes.[11] However, this method uses 5–10 mol% iridium and methylsilanes cannot be selectively borylated in the presence of sterically unhindered aromatic C–H bonds. By contrast, our metal-free, HAT-mediated borylation provided complete selectivity for reaction of α-silyl C(sp^3)–H bonds (**54**-**56**, **62**-**65**) (Fig. 3). In

addition, good functional group tolerance was demonstrated by the successful borylation of substrates containing halides (**56**-**58**, **61**), carboxylate esters (**59**-**66**), enoates (**64**), ketones (**65**), and pinacol boronic esters (**67**). Permethyloligosilanes were also borylated in good yield, including hexamethyldisilane (**68**) and bis(trimethylsilyl)methane (**69**). Interestingly, tetraethylsilane (**70**) reacted selectively at the methylene (α) position, again contrasting the iridium-catalysed selectivity, which gives only the product of methyl (β) borylation.[11] As before, we explored the effect of stoichiometry of organosilane and found that, whilst the yields declined with reduced loading (**54**, **65** and **68**), a 35% yield of boronic ester **54** could still be achieved using the organosilane as the limiting reagent.

To gain insight into the mechanism of this metal-free C–H borylation, we performed a series of experiments to confirm the identity of the HAT species and determine how it is generated. Testing other *N*-alkoxyphthalimides showed that replacing the trifluoroethoxy group of **14** with a phenoxy group caused only a small reduction in reaction efficiency (Table S4). This indicated that alkoxy radicals are unlikely to be responsible for HAT because the relatively weak O–H bond of phenol (BDE = 90 kcal mol^{-1}) makes HAT thermodynamically disfavoured.[25] Instead, the vital role of chloride led us to suspect the involvement of chlorine radicals. This was confirmed upon subjecting 1,6-heptadiene (**71**) to modified reaction conditions using 1 equivalent of ClB(cat), which gave chlorinated (cyclopentylmethyl)boronic ester **72** derived from a chlorine radical addition/5-*exo*-trig cyclisation/borylation sequence (Fig. 4a). Through fluorescence quenching experiments (Fig. S9), we determined that chlorine radicals could be formed via PET between **14** and chloride anions, where photoexcitation of **14** produces a strongly oxidising excited state ($E_{p/2}$ [**14***/**14**$^{\bullet-}$] = 1.46 V vs. saturated calomel electrode (SCE) in MeCN) capable of undergoing exergonic single-electron transfer (SET) with chloride anions ($E_{p/2}$ [$Cl^{\bullet}/Cl^{-}$] = 1.00 V vs. SCE in MeCN for NEt_4Cl). The formation of chloride anions from ClB(cat) was supported by NMR experiments showing hydrolysis of ClB(cat) by trace water in acetonitrile (Figs. S18-S20). Interestingly, fluorescence quenching experiments showed that the excited state of **14** was quenched with similar efficiency by ClB(cat), NEt_4Cl,

and $B_2(cat)_2$ (Figs. S9–S11). As the initial concentration $B_2(cat)_2$ is high with respect to ClB(cat) or chloride anions, the predominant PET process is likely to be between **14** and $B_2(cat)_2$.

Based on these observations, we propose the mechanism outlined in Figure 4b. After photoexcitation of **14** to **73**, reductive quenching by $B_2(cat)_2$ and subsequent β-scission of radical anion **74** gives the trifluoroethoxy radical **75**. Oxygen-centred radicals are known to react with catechol boronic esters to form radical "ate" complexes, where the unpaired electron is delocalised onto the catecholate ligand.[34] Therefore, we propose that chlorine radicals are formed through the reaction of **75** with ClB(cat) via radical "ate" complex **76**. HAT from **15** [BDE = 99 kcal mol^{-1}][35] to either a chlorine radical or complex **76** generates hydrochloric acid [BDE = 103 kcal mol^{-1}][25], alkyl radical **77**, and trifluoroethyl borate **78**. Borylation of **77** with $B_2(cat)_2$ proceeds via radical complex **79**, as previously described by Studer,[31] with cleavage of the B–B bond facilitated by reaction with chloride. As Lewis base adducts of boryl radicals have been reported to be strong single-electron reductants,[36] regeneration of **76** can occur through SET between chloride-stabilised boryl radical **80** and **14** (Figs. S32-S34).

Given that regioselectivities in HAT processes from simple alkanes to chlorine radicals follow the reactivity trend of methine > methylene > methyl,[37] we proceeded to investigate the origin of the unexpected and unique regioselectivity in our borylation reaction. Under our standard conditions, pentane was borylated in a 54:46 primary/secondary ratio. However, the regioselectivity was found to be dependent on the stoichiometry of $B_2(cat)_2$, with higher equivalents leading to increased secondary selectivity (Fig. 4c). Conversely, adding trifluoroethyl borate **78** to the reaction resulted in an increase in primary selectivity. These reactions provide evidence for the regioselectivity being determined during both the HAT and C–B bond forming steps. Higher primary selectivity with lower $B_2(cat)_2$ concentration is indicative of competing reaction pathways for secondary alkyl radical intermediates, whereby a slower rate of borylation for these more hindered radicals results in deleterious pathways (e.g., single-electron oxidation). Higher primary selectivity with higher borate **78** concentration provides indirect evidence for the formation of radical "ate"

complex **76**, which undergoes primary-selective HAT reactions. To probe the high methyl-selectivity for substrates possessing both methylene and methine groups, we performed the borylation of 2,5-dimethylhexane (**82**) in the presence of an alkene radical trap [*N*-methyl-*N*-phenyl-methacrylamide (**83**)] (Fig. 4d). This provided boronic ester **29** in 21% yield with >97:3 methyl (α) selectivity, as well as 3% of oxindole **84**, which was formed with high selectivity for methine (β) C–H functionalisation. This confirms the non-productive formation of sterically hindered secondary and tertiary alkyl radicals. However, the low yield of **84** and the lack of other tertiary radical-derived side-products suggest that the regioselectivity is largely determined during the HAT step. We propose that this is a result of HAT occurring directly to complex **76**, rather than a "free" chlorine radical, where complexation of the chlorine radical with borate **78** makes a more sterically demanding HAT species that is able to selectively functionalise less hindered but stronger C–H bonds,[38] thus providing unusually high primary C–H selectivity.

We have introduced a mechanistically new approach to borylations of non-activated C(sp^3)–H bonds for the synthesis of alkylboronic esters from simple alkanes. By utilising a photoinduced HAT strategy, a broad range of alkanes were borylated under mild conditions and with regioselectivities distinct from those of established metal-catalysed protocols, namely high selectivity for C(sp^3)–H over C(sp^2)–H bonds. The reaction also provides a rare example of a radical-mediated C–H functionalisation proceeding with high selectivity for substitution of methyl C–H bonds over weaker secondary, tertiary, and benzylic C–H bonds. While further developments are needed to improve the modest yields and high substrate loading, this radical-mediated C–H borylation allows transformation of feedstock chemicals into valuable organoboron products with selectivities that complement those of existing methods.

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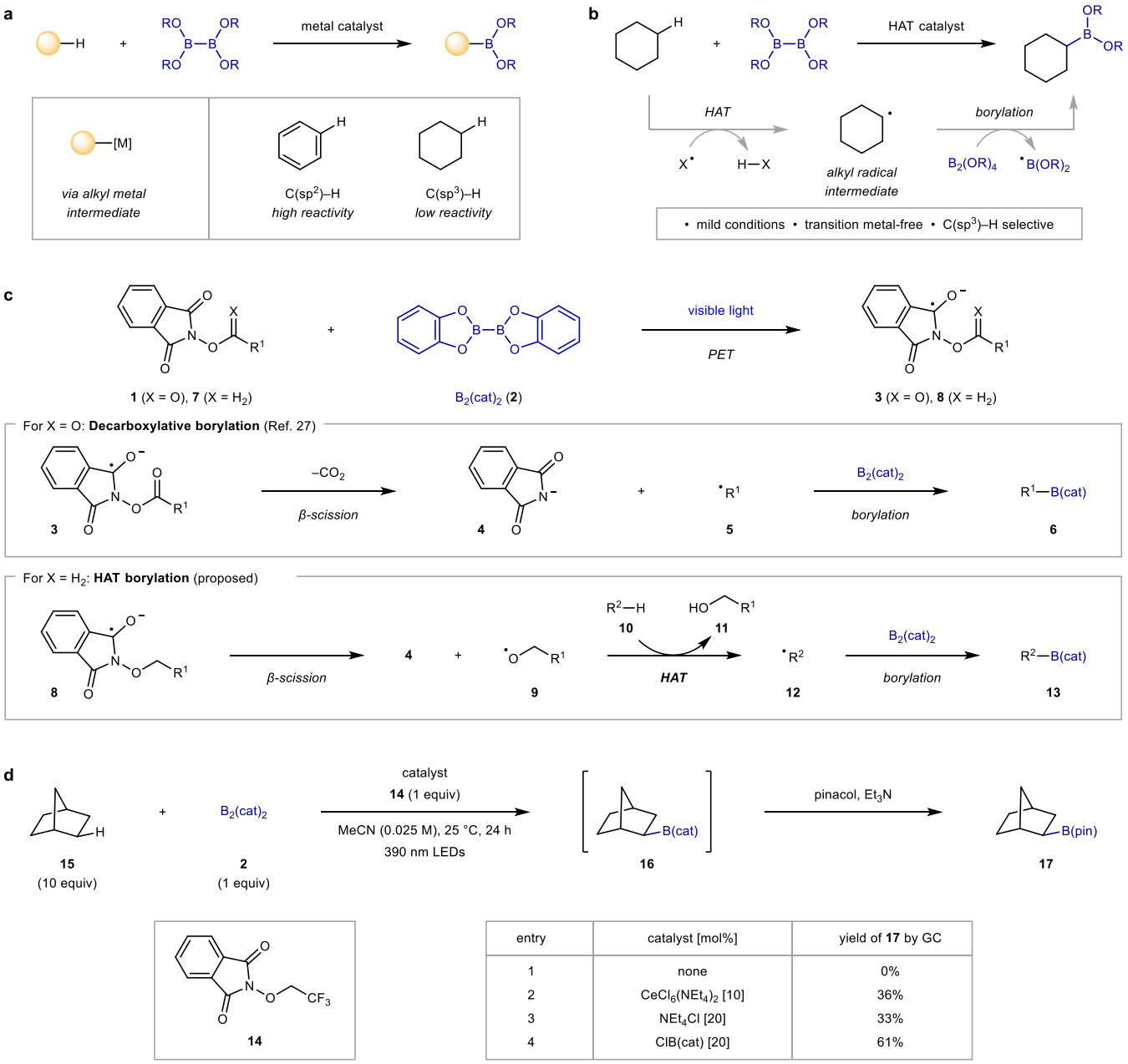
Figure Legends



entry	catalyst [mol%]	yield of **17** by GC
1	none	0%
2	$CeCl_6(NEt_4)_2$ [10]	36%
3	NEt_4Cl [20]	33%
4	ClB(cat) [20]	61%

Fig. 1. Catalytic C–H borylation reactions. a, Transition metal-catalysed C–H borylations. These reactions proceed via cleavage of the C–H bond by the metal catalyst to form alkyl metal intermediates. **b**, Proposed radical-mediated C(sp^3)–H borylation using HAT catalysis. **c**, Photoinduced decarboxylative borylation of *N*-hydroxyphthalimide esters **1**[27] and proposed C(sp^3)–H borylation using *N*-alkoxyphthalimides **7**. **d**, Reaction development. Yields are based on molar equivalents of **2**. LED, light-emitting diode; cat, catecholato; pin, pinacolato.

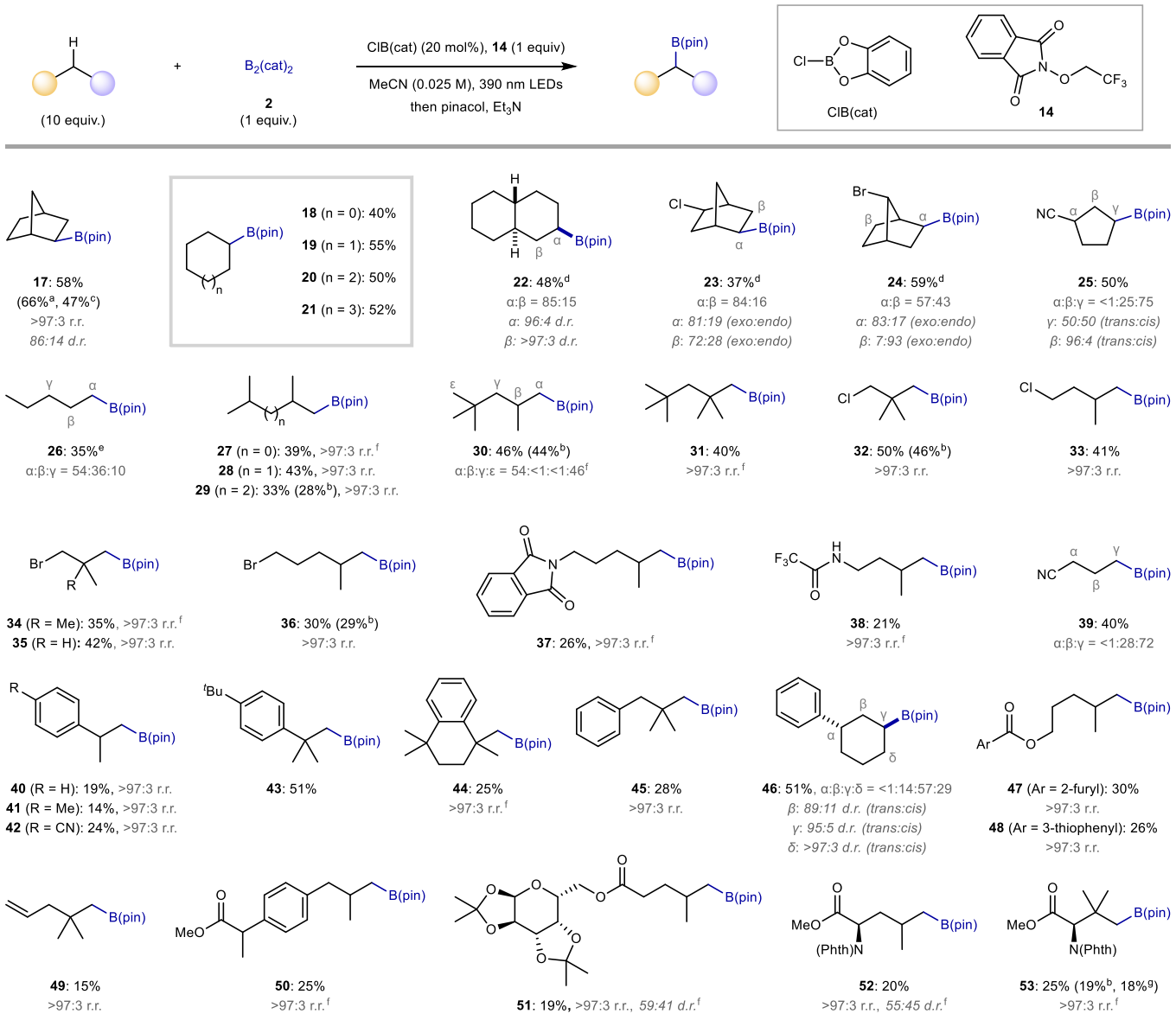


Fig. 2. Photoinduced C–H borylations of alkanes. Reactions were performed with 0.3 mmol of $B_2(cat)_2$. Yields are of isolated products. Regioisomeric ratios (r.r.) and diastereomeric ratios (d.r.) were determined by GC analysis. Numbers in parentheses show yields obtained using different alkane stoichiometry ([a]20 equiv., [b]5 equiv., [c]3 equiv.). [d]The r.r. and d.r. were determined by ^{1}H NMR analysis after oxidation to the corresponding alcohol. [e]The yield was determined by GC analysis. [f]The r.r. and d.r. were determined by ^{1}H NMR analysis. [g]Using 1.0 equiv. alkane and 1.2 equiv. $B_2(cat)_2$. N(Phth), N-phthalimide.

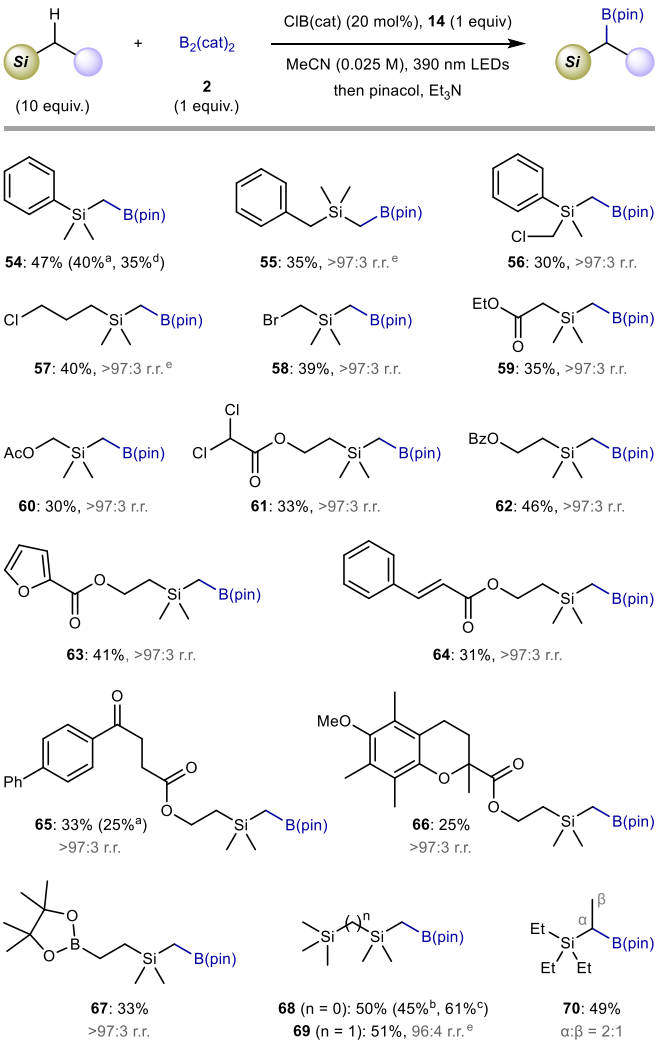


Fig. 3. Photoinduced C–H borylations of silanes. Reactions were performed with 0.3 mmol of $B_2(cat)_2$. Yields are of isolated products. The r.r. was determined by ^{1}H NMR analysis. Numbers in parentheses show yields obtained using different silane stoichiometry ([a]3 equiv., [b]5 equiv., [c]20 equiv.). [d]Using 1.0 equiv. silane and 1.2 equiv. $B_2(cat)_2$. [e]The r.r. was determined by GC analysis.

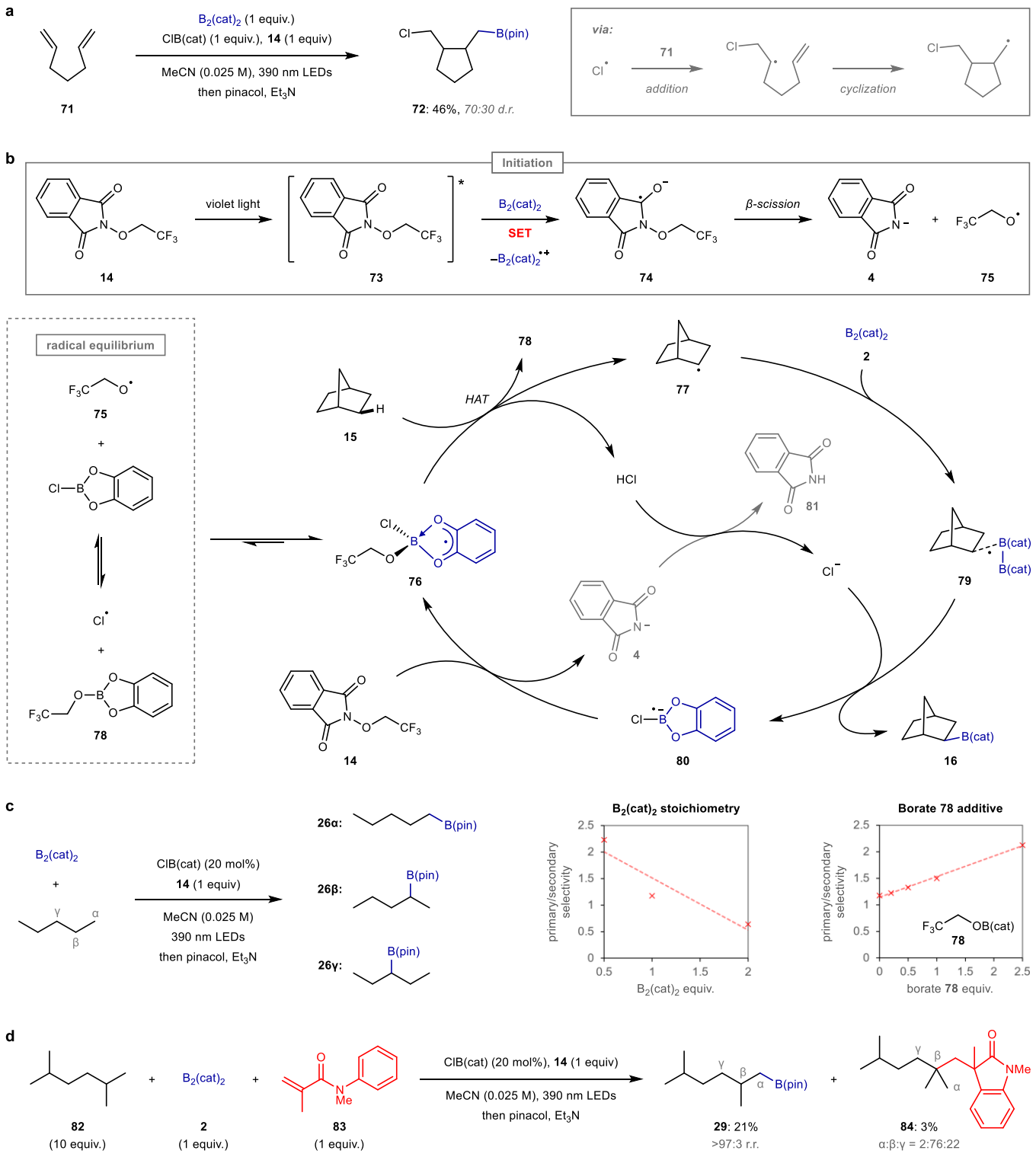


Fig. 4. Mechanistic studies. a, Evidence for the formation of chlorine radicals. **b**, Proposed mechanism. **c**, Effect of $B_2(cat)_2$ and borate **78** concentration on regioselectivity in the borylation of pentane. **d**, Trapping of tertiary and hindered secondary alkyl radicals.

Data availability: Materials and methods, experimental procedures, characterisation data, spectra, and additional mechanistic discussions are available in the Supplementary Information.

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Additional Information:

Supplementary Information is available for this paper.

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